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Commentary

GLP-2 cures the gut – What about the liver?



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Glucagon-like peptide 2 (GLP-2) analogues represent the first medical therapy, which has truly proven to reduce the requirement for parenteral support in patients with intestinal failure due to short bowel syndrome [1]. During GLP-2 treatment, patients with short bowel syndrome show improved intestinal absorption in conjunction with increased villus height, crypt depth and mesenteric blood flow. Despite the well-documented and striking ability of GLP-2 analogues to modulate intestinal physiology, and plethora of previous clinical trials recapitulating the positive effects on intestinal function and parenteral support requirements, very few clinical or experimental studies have addressed consequences of GLP-2 therapy on liver function in short bowel syndrome thus far. This appears rather surprising at a time in which the significance of the gut–liver axis is drawing increasingly attention among research laboratories worldwide in a search of novel therapies for a variety of hepatobiliary diseases.

One of the most significant complications of short bowel syndrome is a unique type of liver injury referred to as intestinal failure associated liver disease (IFALD) without any efficient medical therapy currently available. Liver histology typically features inflammation and cholestasis with variable progression of fibrosis and steatosis, associated with increased biochemical markers of cholestasis and liver injury, while generally accepted diagnostic criteria for IFALD are still missing [2]. Around 25–60% of patients with intestinal failure demonstrate advanced liver fibrosis at the time of assessment for intestinal transplantation [3,4]. IFALD results from combined consequences of compromised intestinal function and parenteral nutrition. Based on a mouse model recapitulating the pathophysiology in humans, biliary secretion of bile acids, sterols and bilirubin is impaired due to suppression of their upstream nuclear receptors, farnesoid X receptor (FXR) and liver X receptor, and respective canalicular bile transporters by macrophages activated synergistically by bowel derived bacterial pathogens and plant sterols, present in all parenteral vegetable oil lipid preparations [5,6]. Surgical resection and inflammation of the ileum further interferes with FXR signaling by interrupting the enterohepatic circulation of bile acids and reducing fibroblast growth factor 19 secretion, which upregulates bile acid synthesis and exacerbates primary bile acid overload induced injury to hepatocytes with malfunctioning canalicular bile secretion [7,8].

To address effects of a novel long-acting GLP-2 analogue, glepaglutide, on the gut–liver axis in patients with short bowel syndrome, Naimi et al. studied markers of liver function, bacterial translocation and macrophage activation in their randomized, double blind, dose-finding, cross-over phase two trial including 16 patients with normal or near normal biochemistry [9]. After three weeks treatment period with 10 mg dose, indocyanine green clearance increased and plasma bilirubin lowered minimally, while plasma alkaline phosphatase decreased in the 1 mg dose group, suggesting a beneficial effect of glepaglutide on hepatic excretory function. Unexpectedly, plasma soluble CD163, a marker for macrophage activation, increased significantly and another surrogate used for macrophage activation, soluble mannose receptor, tended to also increase ($P = .068$) in the 10 mg dose group. The magnitude of the soluble mannose receptor increase was comparable with changes following 0.1 mg dose (0.03 mg/mL; $P = 0.115$). No significant changes occurred in the low base line plasma concentration of lipopolysaccharide binding protein, a surrogate for bacterial translocation, and in liver stiffness, which, if anything, tended to increase in the 10 mg dose group.

Although this study may have produced more questions than answers, authors should be congratulated for addressing hepatobiliary effects and the underlying mechanisms of a GLP-2 analogue in a randomized study design for the first time. While hepatic excretory function seemed to improve during glepaglutide treatment, enhanced liver macrophage activation would be an unwanted harmful effect, which clearly requires careful reassessment in future clinical trials with larger patient cohorts and longer treatment periods. In this respect, it would be valuable to measure serum plant sterol concentrations, while focusing on parenteral nutrition-dependent patients and individuals with established IFALD, who are more likely to exhibit increased liver macrophage activation and bacterial translocation along with raised biochemical markers of cholestasis, including bile acids, already at baseline. Only then, one could really test, whether intestinotrophic properties of glepaglutide would reduce bacterial translocation by improving intestinal epithelial barrier function resulting in decreased macrophage activation and improvement in cholestasis, or unexpectedly, confirm the increased macrophage activation as suggested by the current study. Of note, the three patients with the highest and above normal soluble CD163 concentration at base line were heavily dependent on parenteral support, had a very short remaining intestine ≤ 50 cm and showed increased biochemical markers of cholestasis, hinting that intestinal compromise, parenteral nutrition, macrophage activation and cholestasis

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were linked in these patients. When interpreting the results of Naimi et al., one should also note that indocyanine green clearance may not reliably reflect canalicular bile acid secretion as they seem to utilize different canalicular transporters [10]. Obviously, detailed mechanistic understanding how GLP-2 analogues modulate the gut-liver axis and liver function in short bowel syndrome requires translational basic research. It would be desirable that these models combine parenteral nutrition with extensive bowel resection involving distal small bowel and colon mimicking the underlying pathophysiology frequently encountered in patients.

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